PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DK62208PC	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/011632	International filing date *(day/month/year)* 15.10.2004	Priority date *(day/month/year)* 17.10.2003
International Patent Classification (IPC) or national classification and IPC G01N33/68, C12Q1/68		
Applicant DKFZ DEUTSCHES KREBSFORSCHUNGSZENTRUM...		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.08.2005	25.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Marttin, E Telephone No. +31 70 340-2862

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011632

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-51 as originally filed

Claims, Numbers

1-28 received on 02.09.2005 with letter of 02.08.2005

Drawings, Figures

1-7 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1,2,20,21
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2, 3, 4 in part, 5, 9-10 in part, 11, 12, 13-17 in part, 20-23, 24 in part, 25-28

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 2, 3, 4 in part, 5, 9-10 in part, 11, 12, 13-17 in part, 20-23, 24 in part, 25-28

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 4 in part, 6-8, 9-10 in part, 13-17 in part, 18, 19, 24 in part .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,4,6-10,13,14,17-19,24
	No:	Claims	15,16
Inventive step (IS)	Yes:	Claims	1,4,6-10,13,14,18,19,24
	No:	Claims	15-17
Industrial applicability (IA)	Yes:	Claims	1,4,6-10,13-19,24
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

This report has been established as if some of the amendments had not been made, i.e. the amendments of claims 1, 2, 20 and 21, since the amendment of "at least 5 amino acids in length" does not have a basis in the specification as originally filed (Rule 70.2(c) PCT).

Re Item IV

Lack of unity of invention

1

The following documents are referred to in this communication (for relevant passages see search report):

D1: GILPIN B J ET AL: "A novel, secreted form of human ADAM 12 (Meltrin alpha) provokes myogenesis in vivo" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 273, no. 1, 2 January 1998 (1998-01-02), pages 157-166, XP002229017 ISSN: 0021-9258 cited in the application

D2: KOLBEN M ET AL: "Proteases and their inhibitors are indicative in gestational disease." EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY. IRELAND SEP 1996, vol. 68, no. 1-2, September 1996 (1996-09), pages 59-65, XP002272282 ISSN: 0301-2115

D3: US 2003/170627 A1 (WONG SOPHIA LI-MING ET AL) 11 September 2003 (2003-09-11)

D4: DATABASE WPI Section Ch, Week 198715 Derwent Publications Ltd., London, GB; Class B04, AN 1987-106528 XP002272283 & SU 1 250 257 A (MOSC SECOND MED INS) 15 August 1986 (1986-08-15)

D5: WO 99/46597 A (DIAGNOSTIC SYSTEMS LAB INC) 16 September 1999 (1999-09-16)

D6: LEACH R E ET AL: "Pre-eclampsia and expression of heparin-binding EGF-like growth factor" LANCET, XX, XX, vol. 360, no. 9341, 19 October 2002 (2002-10-19), pages 1215-1219, XP004388635 ISSN: 0140-6736

2

The problem to be solved in the present application relates to the provision of targets for the diagnosis or treatment of preeclampsia and related syndromes.

The subject-matter of claims 1, 4 (partially insofar as dependent on claim 1), 6-8, 9-10 (partially insofar as dependent on claims 1, 6 or 7), 13-17 (partially insofar as related to claims 6-8), 18, 19, 24 (partially insofar as dependent on claim 18) on the one hand and the subject-matter of claims 2, 3, 4 (partially insofar as dependent on claims 2 and 3), 5, 9-10 (partially insofar as dependent on claim 2), 11, 12, 13-17 (partially insofar as related to claims 2-5), 20-23, 24 (partially insofar as dependent on claim 20) and 25-28 on the other hand provide at least two different kinds of solutions therefore.

The subject-matter of claims 1, 4 (partially insofar as dependent on claim 1), 6-8, 9-10 (partially insofar as dependent on claims 1, 6 or 7), 13-17 (partially insofar as related to claims 6-8), 18 and 19, provides through the use of ADAM 12 protein or a nucleic acid molecule with a nucleic acid sequence for ADAM 12 protein for the diagnosis or treatment of preeclampsia and related syndromes, with the inherent structural and functional features of ADAM 12 protein and the nucleic acid sequence of ADAM 12 protein as essential technical features, uses that are alleged to solve the above identified problem. The subject-matter of claims 2, 3, 4 (partially insofar as dependent on claims 2 and 3), 5, 9-10 (partially insofar as dependent on claim 2), 11, 12, 13-17 (partially insofar as related to claims 2-5), 20-23, 24 (partially insofar as dependent on claim 20) and 25-28 provides, through the use of ligands binding to ADAM 12 or inhibitors of ADAM 12, with the inherent structural and functional features of the ligands or inhibitors as essential technical features, uses that are alleged to solve the above identified problem.

However, the special technical feature in the sense of Rule 13.2 PCT of each ADAM 12 protein or nucleic acid sequence of ADAM 12 protein on the one hand or ligand or inhibitor on the other hand is not the same or corresponding for the two groups of inventions.

Independent of the above reasoning, the list of ligands and inhibitors in claims 5 and 22 can be considered to represent a so-called "Markush grouping" in the sense of the Guidelines C-III, 7.4a. As explained in the Guidelines C-III, 7.4a a Markush grouping has to fulfil certain criteria in order to be regarded as being similar of nature. The present Markush group does not fulfil these criteria as it misses a common structure, i.e. a significant structural element that is shared by all alternatives.

Moreover, the common property or activity of the present Markus group of ligands and inhibitors of ADAM 12 is the use of ligands binding to ADAM 12 and inhibitors of ADAM 12 for the diagnosis or treatment of preeclampsia and related syndromes. However, the use of ligands binding to ADAM 12 for the diagnosis of preeclampsia and related syndromes is already known from the following prior art documents:

Document D2 discloses that TIMP-1 is elevated in the case of HELLP syndrome (relevant passages as cited in the search report).

Document D4 (abstract) discloses the prognosis of spontaneous abortion or pregnancy toxosis by measuring alpha2-macroglobulin.

Document D5 discloses a method for detecting IGFBP-3 complex in blood to monitor the clinical status or treatments of individuals affected with fetal growth retardation (relevant passages as cited in the search report).

Document D6 discloses that the level of HB-EGF protein is reduced in preeclamptic pregnancies (relevant passages as cited in the search report).

In the light of D2, and D4-D6, each document if taken alone, the above identified technical feature is not novel and inventive and can thus not be the special technical feature which defines the contribution which each of the claimed inventions considered makes over the prior art (Rule 13.2 PCT). No other technical feature could be identified that forms a

technical relation among each of the separate inventions claimed and which could be considered as special technical feature within the meaning of Rule 13.2 PCT.

As the above mentioned criteria are not fulfilled the different groups of inventions are not considered to be linked by a single general inventive concept as required by Rule 13.1 PCT. Therefore the requirements of unity of invention are not fulfilled.

Consequently the groups of inventions are split up as follows:

1) use of ADAM 12 protein or a nucleic acid molecule with a nucleic acid sequence for ADAM 12 protein for the diagnosis or treatment of preeclampsia and related syndromes (claims 1, 4 in part, 6-8, 9-10 in part, 13-17 in part, 18, 19, 24 in part);
2) use of disintegrin domain metalloproteinase inhibitors, in particular KB-R7785 or a derivative thereof, for diagnosis and treatment of preeclampsia and related syndromes (claims 2, 3, 4 in part, 5, 9-10 in part, 11, 12, 13-17 in part, 20-28 in part);
3) use of a TIMP, in particular TIMP-1, TIMP-2, or TIMP-3, for diagnosis and treatment of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20-28 in part);
4) use of IGFBP-3 or IGFBP-5, for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
5) use of HB-EGF for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
6) use of alpha2-macroglobulin for diagnosis and treatment of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20-28 in part);
7) use of PKC-delta for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
8) use of alpha-actinin or alpha-actinin-2 for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
9) use of src for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
10) use of Grb-2 for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
11) use of syndecan-4 for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
12) use of antibodies against ADAM 12, for diagnosis and treatment of preeclampsia and

related syndromes, or use of nucleic acid or protein aptamers for diagnosis of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20-28 in part);
13) use of P-LAP for diagnosis and treatment of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part);
14) use of ligands against ADAM 12 or inhibitors of ADAM 12, insofar as not comprised in the subjects 1-13 mentioned above, for diagnosis and treatment of preeclampsia and related syndromes (claims 2-5 in part, 9-17 in part, 20 in part, 21 in part, 23-28 in part).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1
Document D1 discloses (the references in parentheses applying to this document): Isolated human ADAM 12 cDNA clones.

1.1
INDEPENDENT CLAIM 1, 6, 7, 13 AND 14

1.1.1
Document D2, which is considered to represent the most relevant state of the art, discloses that metalloproteinases are indicative in gestational disease, TIMP-1 and MMP-8 is increased in patients with pathological Doppler flow results, MMP-9 is decreased in preeclampsia and patients with pathological Doppler flow results, and TIMP-1 is elevated in HELLP from which the subject-matter of claims 1, 6, 7, 13 and 14 differs in that ADAM 12 is disclosed.

1.1.2
The problem to be solved by the present invention may therefore be regarded as the provision of an alternative improved marker for the diagnosis of preeclampsia and related disorders / eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

1.1.3
The solution to this problem proposed in claims 1, 6, 7, 13 and 14 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

It would not be obvious to replace the metalloproteases of D2 with the ADAM 12 isoform based on D1 or D3, which suggest that ADAM 12 is a metalloprotease that is found in pregnancy, or that ADAM 12 gene expression plays a role in pregnancy, since document D2 and example 8 of the present application teach away from using any metalloprotease for the diagnosis of preeclampsia or related syndromes, since the metalloprotease MMP-8 is not increased in patients with preeclampsia in D2, nor are ADAM 6 or ADAM 9 expressed at a significantly higher level in preeclamptic patients in example 8 of the present application. The proposed solutions in independent claims 1, 6, 7, 13 and 14 is thus considered to be inventive (Article 33(3) PCT).

1.2
DEPENDENT CLAIMS 4, AND 8-10

Claim 4 is dependent on claim 1, and claim 8-10 are dependent on claim 1 or 6, and as such also meet the requirements of the PCT with respect to novelty and inventive step.

1.3
INDEPENDENT CLAIM 15 AND 16

1.3.1
As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 15. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

1.3.2
The same applies mutatis mutandis to the subject-matter of independent claim 16. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

1.3.3

DEPENDENT CLAIM 17

Dependent claim 17 does not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

2
INDEPENDENT CLAIM 18

2.1
Document D3, which is considered to represent the most relevant state of the art, discloses that the expression of the gene for ADAM 12 and the protein ADAM 12 (meltrin-L in D3) could play an important role in pregnancy and in disorders which affect the fetus and/or the mother, particularly pregnancy-induced hypertension and preeclampsia.

From this, the subject-matter of independent claim 18 differs in that: treatment of preeclampsia with a nucleic acid with a sequence of SEQ ID 1 or 3, a fragment, an antisense sequence, or a RNA sequence thereof is disclosed.

2.1.1
The subject-matter of claim 18 is therefore novel (Article 33(2) PCT) The problem to be solved by the present invention may be regarded as: the provision of a method of treatment of preeclampsia or related syndromes.

2.1.2
The solution to this problem proposed in claim 18 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: it is neither hinted nor suggested in D3 that a nucleic acid with a sequence of SEQ ID 1 or 3, a fragment, an antisense sequence, or a RNA sequence thereof, could be used for the treatment of preeclampsia or related syndromes.

2.2
DEPENDENT CLAIMS 19 AND 24

Claims 19, 24 are dependent on claim 18 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Re Item VIII

Certain observations on the international application

1
CLARITY

1.1
The invention is not sufficiently disclosed since the application describes only the diagnosis of preeclampsia and related syndromes, but does not contain specific embodiments for treatment of preeclampsia and related syndromes (Rule 5.1(a)(v) PCT and Guidelines C-II, 4.9). Furthermore, claims 18, 19 and 24 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description, which only describes diagnosis of preeclampsia and related syndromes. The statements on page 29 - page 36 of the description are considered to be assertions having no technical content, therefore they cannot provide a basis for support of claims 18 and 19 (Guidelines C-III, 6.3). It appears therefore that the invention of the present application could only be performed and repeated with application of inventive skill and with undue burden.

1.2
The terms "related syndrome", "fragment", "being part of", and "located in" used in claim 1 as filed originally are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear Article 6 PCT.

1.3
The embodiments of the invention described on pages 20-22, in particular on page 20, lines 30-32, page 21, lines 2-3 and lines 20-29, and on page 22, lines 14-16 do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the

claims unclear, Article 6 PCT.

Patent Claims

1. Use of the expression level of a peptide or polypeptide with a sequence selected from the group consisting of

    a) an amino acid sequence as presented in SEQ ID NO: 2 or 4;
    b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues;
    c) a fragment of any of the sequences defined above which is at least 5 amino acids in length

    for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

2. Use of a ligand binding specifically to a peptide or polypeptide with a sequence selected from the group consisting of

    a) an amino acid sequence as presented in SEQ ID NO: 2 or 4;
    b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues;
    c) a fragment of any of the sequences defined above which is at least 5 amino acids in length

    for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

3. The use according to claim 2, wherein the ligand is used for measurement of the expression level of the peptide or polypeptide.

4. The use according to any of claims 1 to 3, wherein the sequence is selected from SEQ ID NO: 8.

5. The use according to any of claims 2 to 4, wherein the ligand is selected from the group consisting of

    a) KB-R7785 or a derivative thereof;

b) TIMP-1, TIMP-2, TIMP-3, IGFBP-5, PKC-δ, α-actinin, α-actinin-2, src, Grb-2, or syndecan-4
c) antibodies;
d) nucleic acid or protein aptamers;
e) fragments or derivatives of any of the substances defined in b), c), or d).

6. Use of the expression level of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
b) a nucleic acid with a sequence that exhibits a sequence identity with any of the sequences defined in a) of at least 70% over 300 residues;
c) a nucleic acid which is capable of hybridizing with the nucleic acid as defined in a), or b) under conditions of medium or high stringency;
d) a nucleic acid with the antisense-sequence of any of the sequences defined in a), b) or c);
e) a fragment of any of the nucleic acids as defined in a), b), c), or d), wherein the fragment is at least 15 nucleotides in length;
f) an RNA corresponding to any of the sequences defined in a), b), c), d) or e);

for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

7. Use of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
b) a nucleic acid with a sequence that exhibits a sequence identity with any of the sequences defined in a) of at least 70% over 300 residues;
c) a nucleic acid which is capable of hybridizing with the nucleic acid as defined in a), or b) under conditions of medium or high stringency;
d) a nucleic acid with the antisense-sequence of any of the sequences defined in a), b) or c);
e) a fragment of any of the nucleic acids as defined in a), b), c), or d), wherein the fragment is at least 15 nucleotides in length;
f) an RNA corresponding to any of the sequences defined in a), b), c), d) or e);

for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

8. The use according to any of claims 6 to 8, wherein the fragment has a sequence consisting of SEQ ID NO: 7, 13, 14, 15, 16, 5, 10, 11, or 12 or wherein the fragment has the sequence of a fragment thereof with at least 15 nucleotides in length.

9. The use according to any of claims 1 to 8, wherein the expression level, ligand, or nucleic acid is used in conjunction with a means or a diagnostic agent for the measurement of expression of any of the genes or proteins selected from the group consisting of

a) EPAS-1/HIF-2α,
b) neurokinin B
c) TIMP-1,
d) VEGFR-1,
e) VEGF,
f) IGFBP-1
g) IGFBP-3,
h) matrix metalloproteinase-2,
i) leptin,
j) PAI-1,
k) IGF-1,
l) angiopoetin-2,
m) decorin,
n) PlGF,
o) HLA-G
p) HB-EGF
q) TGF-β3
r) MIFR-2
s) LIM
t) EBI3

and/or diagnostic tools for the measurement of blood pressure or protein content of the urine.

10. The use according to any of claims 2 to 9, wherein the nucleic acid, ligand or, additionally, diagnostic agent is present on an array.

11. Use of the nucleic acid molecule as defined in any of claims 6 to 8, or of a peptide or polypeptide comprising a peptide or polypeptide as defined in any of claims 1 to 4 for the identification of ligands binding specifically to said nucleic acid, peptide or polypeptide.

12. A method for the identification of ligands binding specifically to a peptide or polypeptide as defined in in any of claims 1 to 4, comprising the following steps:

    a) contacting the polypeptide with at least one candidate for a ligand;
    b) measuring the binding of the candidate for a ligand to the polypeptide.

13. A method for the diagnosis of a disease selected from preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes comprising the following steps:

    a) bringing a biopsy or bodily fluid sample into contact with a nucleic acid as defined in any of claims 6 to 8 or a specifically binding ligand as defined in claims 2 to 5, and
    b) detecting the binding of the nucleic acid or ligand.

14. Use of a nucleic acid as defined in any of claims 6 to 8, or a ligand as defined in any of claims 2 to 5, optionally in combination with a diagnostic agent or diagnostic tool as defined in claim 9, for the manufacture of a diagnostic for the diagnosis of a disease selected from preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

15. A diagnostic containing a nucleic acid or ligand, or, additionally, diagnostic agent or tool as defined in any of claims 2 to 9.

16. A diagnostic kit containing a nucleic acid or ligand as defined in any of claims 2 to 9.

17. The diagnostic or diagnostic kit according to any of claims 15 to 16, wherein the nucleic acid, ligand or, additionally, diagnostic agent is present on an array.

18. Use of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
b) a fragment of any of the nucleic acids as defined in a), wherein the fragment is at least 15 nucleotides in length;
c) a nucleic acid with the antisense sequence of any of the sequences defined in a), or b);
d) single-stranded or double-stranded RNA, preferably siRNA, with a sequence corresponding to any of the sequences defined in a), b), or c);

for the manufacture of a medicament for the treatment of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

19. The use according to claim 18, wherein the fragment consists of SEQ ID NO: 5 or 7 or of a fragment thereof wherein the fragment is at least of 15 nucleotides in length.

20. Use of an inhibitor of the biological activity of a peptide or polypeptide with a sequence selected from the group consisting of

a) an amino acid sequence as presented in SEQ ID No. 2 or 4;
b) an amino acid sequence exhibiting a sequence identity with any of the sequences according to a) of at least 85% over 100 residues;
c) a fragment of any of the sequences as defined above wherein the fragment is at least of 5 amino acids in length.

for the manufacture of a medicament for the treatment of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes.

21. The use according to claim 20, wherein the fragment has a sequence consisting of SEQ ID NO: 8 or of a fragment thereof wherein the fragment is at least of 5 amino acids in length.

22. The use according to any of claims 20 to 21, wherein the inhibitor is a disintegrin domain metalloproteinase inhibitor, particularly KB-R7785, a TIMP, particularly TIMP-3 or a fragment thereof, α_2-Macroglobulin, or an antibody directed against ADAM 12.

23. The use according to any of claims 20 to 22, wherein additionally HB-EGF is used for the manufacture of the medicament.

24. The use according to any of claims 18 to 23, wherein the medicament is for treatment of symptoms of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, gestational diabetes, particularly for treatment or prevention of intravascular coagulation, blood platelet destruction, placental abruption, or high blood pressure.

25. Use of a nucleic acid, peptide, or polypeptide as defined in any of claims 1 to 8 for identification of an inhibitor of said nucleic acid, peptide or polypeptide, particularly for identification of an inhibitor of the proteolytic activity or substrate-binding acitivity of said peptide or polypeptide.

26. A method for identification of an inhibitor of the biological activity of a peptide or polypeptide as defined in any of claims 20 to 21, comprising the following steps:

    a) contacting said peptide or polypeptide with a suitable substrate, e.g. HB-EGF,
    b) measuring the decrease in processing of the substrate in the presence as compared to the absence of a candidate for an inhibitor molecule

27. The method according to claim 26, wherein the candidate for an inhibitor is a substrate or a ligand of a peptide or polypeptide as defined in any of claims 1 to 4.

28. A method for the preparation of a pharmaceutical composition, wherein an inhibitor of the nucleic acids, peptides, or polypeptides as defined in any of claims 18 to 21 is identified according to the methods as defined in claim 26 or 27, synthesized in adequate amounts, and formulated into a pharmaceutical composition.